Nipah virus envelope-pseudotyped lentiviruses efficiently target ephrinB2-positive stem cell populations in vitro and bypass the liver sink when administered in vivo.

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Public Summary:
Sophisticated retargeting systems for lentiviral vectors have been developed in recent years. Most seek to suppress the viral envelope's natural tropism while modifying the receptor-binding domain such that its tropism is determined by the specificity of the engineered ligand-binding motif. Here we took advantage of the natural tropism of Nipah virus (NiV), whose attachment envelope glycoprotein has picomolar affinity for ephrinB2, a molecule proposed as a molecular marker of "stemness" (present on embryonic, hematopoietic, and neural stem cells) as well as being implicated in tumorigenesis of specific cancers. NiV entry requires both the fusion (F) and attachment (G) glycoproteins. Truncation of the NiV-F cytoplasmic tail (T5F) alone, combined with full-length NiV-G, resulted in optimal titers of NiV-pseudotyped particles (NiVpp) (approximately 10(6) IU/ml), even without ultracentrifugation. To further enhance the infectivity of NiVpp, we engineered a hyperfusogenic NiV-F protein lacking an N-linked glycosylation site (T5FDeltaN3). T5FDeltaN3/wt G particles exhibited enhanced infectivity on less permissive cell lines and efficiently targeted ephrinB2(+) cells even in a 1,000-fold excess of ephrinB2-negative cells, all without any loss of specificity, as entry was abrogated by soluble ephrinB2. NiVpp also transduced human embryonic, hematopoietic, and neural stem cell populations in an ephrinB2-dependent manner. Finally, intravenous administration of the luciferase reporter NiVpp-T5FDeltaN3/G to mice resulted in signals being detected in the spleen and lung but not in the liver. Bypassing the liver sink is a critical barrier for targeted gene therapy. The extraordinary specificity of NiV-G for ephrinB2 holds promise for targeting specific ephrinB2(+) populations in vivo or in vitro.

Scientific Abstract:
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